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Antibiotic Resistance- Reasons and Control Measures

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Abstract

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes. This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics. Here we report reasons of drug resistance and their prelavance. This review tells conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Keywords

Antibiotics, drug resistance, Human and animal health.

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INTRODUCTION

It is a specific type of drug resistance. Antibiotic resistance evolves naturally via natural selection through random mutation, but it could also be engineered by applying an evolutionary stress on a population. Once such a gene is generated, bacteria can then transfer the genetic information in a horizontal fashion (between individuals) by plasmid exchange. If a bacterium carries several resistance genes, it is called multi resistant or, informally, a superbug. Causes of antibiotic resistance can also be introduced artificially into a microorganism through transformation protocols. This can be a useful way of implanting artificial genes into the microorganism. Antibiotic resistance is a consequence of evolution via natural selection. The antibiotic action is an environmental pressure; those bacteria which have a mutation allowing them to survive will live on to reproduce. They will then pass this trait to their offspring, which will be a fully resistant generation. Several studies have demonstrated that patterns of antibiotic usage greatly affect the number of resistant organisms which develop. Overuse of broad-spectrum antibiotics, such as second- and third-generation cephalosporins, greatly hastens the development of methicillin resistance. Other factors contributing towards resistance include incorrect diagnosis, unnecessary prescriptions, improper use of antibiotics by patients, and the use of antibiotics

as livestock food additives for growth promotion. Researchers have recently demonstrated the bacterial protein LexA may play a key role in the acquisition of bacterial mutations. Resistant pathogens Staphylococcus aureus (colloquially known as "Staph aureus" or a Staph infection) is one of the major resistant pathogens found on the mucous membranes and the skin of around a third of the population, it is extremely adaptable to antibiotic pressure. It was the first bacterium in which penicillin resistance was found—in 1947, just four years after the drug started being mass-produced. Methicillin was then the antibiotic of choice, but has since been replaced by oxacillin due to significant kidney toxicity. MRSA (methicillin-resistant Staphylococcus aureus) was first detected in Britain in 1961 and is now "quite common" in hospitals. MRSA was responsible for 37% of fatal cases of blood poisoning in the UK in 1999, up from 4% in 1991. Half of all S. aureus infections in the US are resistant to penicillin, methicillin, tetracycline and erythromycin. This left vancomycin as the only effective agent available at the time. However, strains with intermediate (4-8 ug/ml) levels of resistance, termed GISA (glycopeptide intermediate Staphylococcus aureus) or VISA (vancomycin intermediate Staphylococcus aureus), began appearing the late 1990s. The first identified case was in Japan in 1996, and strains have since been found in hospitals in England, France and the US. The first documented strain with complete (>16ug/ml) resistance to vancomycin, termed VRSA (Vancomycin-resistant Staphylococcus aureus) appeared in the United States in 2002. A new class of antibiotics, oxazolidinones, became available in the 1990s, and the first commercially available oxazolidinone, linezolid, is comparable to vancomycin in effectiveness against MRSA. Linezolid-resistance in Staphylococcus aureus was reported in 2003. CA-MRSA (Community-acquired MRSA) has now emerged as an epidemic that is responsible for rapidly progressive, fatal diseases including necrotizing pneumonia, severe sepsis and necrotizing fasciitis. Methicillin-resistant Staphylococcus aureus (MRSA) is the most frequently identified antimicrobial drug-resistant pathogen in US hospitals. The epidemiology of infections caused by MRSA is rapidly changing. In the past 10 years, infections caused by this organism have emerged in the community. The 2 MRSA clones in the United States most closely associated with community outbreaks, USA400 (MW2 strain, ST1 lineage) and USA300, often contain Panton-Valentine leukocidin (PVL) genes and more frequently, have been associated with skin and soft tissue infections. Outbreaks of community-associated (CA)-MRSA infections have been reported in correctional facilities, among athletic teams, among military recruits, in newborn nurseries, and among active homosexual men. CA-MRSA infections now appear to be endemic in many urban regions and cause most CA-S. aureus infections. Enterococcus faecium is another superbug found in hospitals. Penicillin-Resistant Enterococcus was seen in 1983, Vancomycin-Resistant Enterococcus (VRE) in 1987, and Linezolid-Resistant Enterococcus (LRE) in the late 1990s. Streptococcus pyogenes (Group A Streptococcus: GAS) infections can usually be treated with many different antibiotics. Early treatment may reduce the risk of death from invasive group a streptococcal disease. However, even the best medical care does not prevent death in every case. For those with very severe illness, supportive care in an intensive care unit may be needed. For persons with necrotizing fasciitis, surgery often is needed to remove damaged tissue. Strains of S. pyogenes resistant to macrolide antibiotics have emerged, however all strains remain uniformly sensitive to penicillin. Resistance of Streptococcus pneumoniae to penicillin and other beta-lactams is increasing worldwide. The major mechanism of resistance involves the introduction of mutations in genes encoding penicillin-binding proteins. Selective pressure is thought to play an important role, and use of beta-lactam antibiotics has been implicated as a risk factor for infection and colonization. Streptococcus pneumoniae is responsible for pneumonia, bacteremia, otitis media, meningitis, sinusitis, peritonitis and arthritis.

Reasons of the Antibiotic Resistance:

1. Over usage or over prescription of antibiotics
2. Inappropriate prescription.
3. Availability of new drugs.
4. Antibiotic resistant bacteria cultures.

1. Over usage or Over-prescription of Antibiotics:

As early as 1945, Sir Alexander Fleming raised the alarm regarding antibiotic overuse when he warned that the “public will demand [the drug and] … then will begin an era … of abuses [7, 14]. The overuse of antibiotics clearly drives the evolution of resistance[5, 9] Epidemiological studies have demonstrated a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacteria strains[10]. In bacteria, genes can be inherited from relatives or can be acquired from nonrelatives on

mobile genetic elements such as plasmids[9]. This horizontal gene transfer (HGT) can allow antibiotic resistance to be transferred among different species of bacteria.[9] Resistance can also occur spontaneously through mutation[9]. Antibiotics remove drug-sensitive competitors, leaving resistant bacteria behind to reproduce as a result of natural selection.[9] Despite warnings regarding overuse, antibiotics are overprescribed worldwide. 10 In the U.S., the sheer number of antibiotics prescribed indicates that a lot of work must be done to reduce the use of these medications[12]. An analysis of the IMS Health Midas database, which estimates antibiotic consumption based on the volume of antibiotics sold in retail and hospital pharmacies, indicated that in 2010, 22.0 standard units (a unit equalling one dose, i.e., one pill, capsule, or ampoule) of antibiotics were prescribed per person in the U.S.17 The number of antibiotic prescriptions varies by state, with the most written in states running from the Great Lakes down to the Gulf Coast, whereas the West Coast has the lowest use [5,12]. In some states, the number of prescribed courses of treatment with antibiotics per year exceed the population, amounting to more than one treatment per person per year[12] In many other countries, antibiotics are unregulated and available over the counter without a prescription [10,15]. This lack of regulation results in antibiotics that are easily accessible, plentiful, and cheap, which promotes overuse.[15] The ability to purchase such products online has also made them accessible in countries where antibiotics are regulated[15].

2. Inappropriate Prescribing:

Incorrectly prescribed antibiotics also contribute to the promotion of resistant bacteria. 5 Studies have shown that treatment indication, choice of agent, or duration of antibiotic therapy is incorrect in 30% to 50% of cases [5,18] One U.S. study reported that a pathogen was defined in only 7.6% of 17,435 patients hospitalized with community-acquired pneumonia (CAP)[14] In comparison, investigators at the Karolinska Institute in Sweden were able to identify the probable pathogen in 89% of patients with CAP through use of molecular diagnostic techniques (polymerase chain reaction [PCR] and semi quantitative PCR)[14]. In addition, 30% to 60% of the antibiotics prescribed in intensive care units (ICUs) have been found to be unnecessary, inappropriate, or suboptimal.[18] incorrectly prescribed antibiotics has questionable therapeutic benefit and expose patients to potential complications of antibiotic therapy[11]. Sub inhibitory and sub therapeutic anti the Antibiotic Resistance Crisis, Part 1: Causes and Threats the frequency with which doctors prescribe antibiotics varies greatly from state to state. The reasons for this variation are being studied and might suggest areas where improvements in antibiotic prescribing (fewer unnecessary prescriptions) would be most helpful Low levels of antibiotics have been shown to contribute to strain diversification in organisms such as Pseudomonas aeruginosa. 8 Sub inhibitory concentrations of piperacillin and/or tazobactam have also been shown to induce broad proteomic alterations in Bacteroides fragilis.

3. Availability of Few New Antibiotics:

The development of new antibiotics by the pharmaceutical industry, a strategy that had been effective at combating resistant bacteria in the past, had essentially stalled due to economic and regulatory obstacles (Figure 3)[14] Of the 18 largest pharmaceutical companies[15] abandoned the antibiotic field[14] Mergers between pharmaceutical companies have also substantially reduced the number and diversity of research teams[13]. Antibiotic research conducted in academia has been scaled back as a result of funding cuts due to the economic crisis.[13] Antibiotic development is no longer considered to be an economically wise investment for the pharmaceutical industry [14]. Because antibiotics are used for relatively short periods and are often curative, antibiotics are not as profitable as drugs that treat chronic conditions, such as diabetes, psychiatric disorders, asthma, or gastroesophageal reflux[1–3, 13, 14]. A cost–benefit analysis by the Office of Health Economics in London calculated that the net present value (NPV) of a new antibiotic is only about $50 million, compared to approximately $1 billion for a drug used to treat a neuromuscular disease [14]. Because medicines for chronic conditions are more profitable, pharmaceutical companies prefer to invest in them. 2 Another factor that causes antibiotic development to lack economic appeal is the relatively low cost of antibiotics. Newer antibiotics are generally priced at a maximum of $1,000 to $3,000 per course compared with cancer chemotherapy that costs tens of thousands of dollars[23, 13, 14]. The availability, ease of use, and generally low cost of antibiotics has also led to a perception of low value among payers and the public[13]. In addition, microbiologists and infectious-disease specialists have advised restraint regarding antibiotic use[13]. Therefore, once a new antibiotic is marketed, physicians—rather than prescribing it immediately—often hold this new agent in reserve for only the worst cases due to fear of promoting drug resistance.

The Antibiotic Resistance Crisis, Part 1: Causes and Threats Number of Antibacterial New Drug Application Approvals Versus Year Intervals The number of new antibiotics developed and approved has decreased steadily over the past three decades (although four new drugs were approved in 2014), leaving fewer options to treat resistant bacteria. *Drugs are limited to systemic agents. Data courtesy of the CDC5 and the FDA Center for Drug Evaluation and Research. 1980– 1984 1985– 1989 1990– 1994 1995– 1999 2000– 2004 2005– 2009 2010– 2014 280 P&T® • April 2015 • Vol. 40 No. 4 tance, and they continue to prescribe older agents that have shown comparable efficacy [1,2]. Therefore, new antibiotics are often treated as "last-line" drugs to combat serious illnesses[1, 2]. This practice leads to the reduced use of new antibiotics and a diminished return on investment[13]. When new agents are eventually used, the emergence of resistance is nearly inevitable. However, since bacterial evolution is uncertain, the timeline for the development of resistance is unpredictable. 2 A manufacturer that invests large sums of money into antibiotic development may therefore discover that profits are prematurely curtailed when resistance develops to a new antibiotic. 2 Economic uncertainty related to the Great Recession has also had a restraining effect on the end users of antibiotics. 2 Developed countries with well-funded health care systems have applied austerity measures, while developing countries such as China and India still have a large cohort of population that cannot afford expensive new medicines[2]. As an additional complication, most antibiotics are currently off patent and are supplied by manufacturers of generic drugs.3 The result has been access to cheap and generally effective drugs, which is good for the public; however, the downside is that many payers expect all antibiotics to be priced similarly—even new agents that target multidrug-resistant (MDR) pathogens. 3 Because of these factors, many large pharmaceutical companies fear a potential lack of return on the millions of U.S. dollars that would be required to develop a new antibiotic[1, 2, 13]. The Infectious Diseases Society of America (IDSA) reported that as of 2013, few antibacterial compounds were in phase 2 or 3 development [11, 14]. In particular, the IDSA noted that unacceptably few agents with activity against emerging, extensively resistant gram-negative bacteria, such as Enterobacteriaceae, Pseudomonas aeruginosa, and Acinetobacter baumannii, were being developed[11]. Pharmaceutical companies have also taken a more active interest in developing antibiotics for methicillin-resistant Staphylococcus aureus (MRSA), rather than gram-negative pathogens[2]. The most likely explanation for this imbalance is that MRSA is a major problem worldwide, whereas the market for treating gram-negative organisms is smaller and somewhat more unpredictable given that resistance is rapidly acquired.

4. Antibiotic-Resistant Bacterial Infections:

Antibiotic-resistant infections are already widespread in the across the globe. 1 A 2011 national survey of infectious disease specialists, conducted by the IDSA Emerging Infections Network, found that more than 60% of participants had seen a pan-resistant, untreatable bacterial infection within the prior year. 7 Many public health organizations have described the rapid emergence of resistant bacteria as a "crisis" or "nightmare scenario" that could have "catastrophic consequences." 8 The CDC declared in 2013 that the human race is now in the "post-antibiotic era," and in 2014, the World Health Organization (WHO) warned that the antibiotic resistance crisis is becoming dire. 15 MDR bacteria have been declared a substantial threat to U.S. public health and national security by the IDSA and the Institute of Medicine, as well as the federal Interagency Task Force on Antimicrobial Resistance[1] Among gram-positive pathogens, a global pandemic of resistant S. aureus and Enterococcus species currently poses the biggest threat [5, 16]. MRSA kills more Americans each year than HIV/AIDS, Parkinson's disease, emphysema, and homicide combined[1, 12]. Vancomycin-resistant enterococci (VRE) and a growing number of additional pathogens are developing resistance to many common antibiotics[1]. The global spread of drug resistance among common respiratory pathogens, including Streptococcus pneumoniae and Mycobacterium tuberculosis, is epidemic. 16 Gram-negative pathogens are particularly worrisome because they are becoming resistant to nearly all the antibiotic drug options available, creating situations reminiscent of the pre-antibiotic era[1, 5, 16]. The emergence of MDR (and increasingly pan-resistant) gram-negative bacilli has affected practice in every field of medicine.[1] The most serious gram negative infections occur in health care settings and are most commonly caused by Enterobacteriaceae (mostly Klebsiella pneumoniae), Pseudomonas aeruginosa, and Acinetobacter[5,16]. MDR gram-negative pathogens are also becoming increasingly prevalent in the community[16]. These include extended spectrum beta-lactamase-producing Escherichia coli and Neisseria gonorrhoeae[16]. The CDC assessed

antibiotic-resistant bacterial infections according to seven factors: clinical impact, economic impact, incidence, 10-year projection of incidence, transmissibility, availability of effective antibiotics, and barriers to prevention[5]. The threat level of each bacteria was then classified as "urgent," "serious," or "concerning" (Table 1).[16]. In general, threats that are urgent or serious require more monitoring and prevention activities, whereas those considered concerning require less[5]. A summary of information regarding the resistant bacteria mentioned above follows. Information regarding other strains of resistant bacteria that have been identified as threats by the CDC can be found at http://www.cdc.gov/drugresistance/ threat-report-2013/pdf/ar-threats-2013-508.pdf.5

Examples for antibiotic resistant species:

- Methicillin-Resistant Staphylococcus Aureus
- Vancomycin-Resistant Enterococci
- Drug-Resistant Streptococcus pneumoniae
- Drug-Resistant Mycobacterium Tuberculosis
- Carbapenem-Resistant Enterobacteriaceae(CRE)

The Clinical and Economic Burden of Antibiotic resistance:

Antibiotic-resistant infections are a substantial health and economic burden to the health care system, as well as to patients and their families[1]. They commonly occur in hospitals, due to the clustering of highly vulnerable patients, extensive use of invasive procedures, and high rates of antibiotic use in this setting[1]. Nearly two million Americans per year develop HAIs, resulting in 99,000 deaths, most due to antibacterial resistant pathogens [1]. In 2006, two common HAIs (sepsis and pneumonia) were found to be responsible for the deaths of nearly 50,000 Americans and cost the U.S. health care system more than $8 billion1. Antibiotic-resistant infections add considerable costs to the nation's already overburdened health care system. When first-line and then second-line antibiotic treatment options are limited or unavailable, health care professionals may be forced to use antibiotics that are more toxic to the patient and frequently more expensive [5, 11]. Even when effective treatments exist, data show that in most cases patients with resistant infections require significantly longer hospital stays, more doctor's visits, and lengthier recuperations and experience a higher incidence of long-term disability. 5 The duration of hospital stays for patients with antibiotic-resistant infections was found to be prolonged by 6.4 to 12.7 days, collectively adding an extra eight million hospital days.[1] Estimates regarding the medical cost per patient with an antibiotic-resistant infection range from $18,588 to $29,069 [1,14]. The total economic burden placed on the U.S. economy by antibiotic-resistant infections has been estimated to be as high as $20 billion in health care costs and $35 billion a year in lost productivity.[1] Antibiotic-resistant infections also burden families and communities due to lost wages and health care costs[1, 15]

Table 1: Table representing the mechanism of drug resistance of common antibiotics:

Antibiotics	Examples	Mode(s) of resistance
P-Lactums	Penicillins ,Cephalosporins, Penems, Monobactams	Hydrolysis, efflux, altered target
Aminoglycosides	Gentamicin, Streptomycin, Spectinomycin	Phosphorylation, acetylation, nucleotidylation, efflux, altered target
Glycopeptides	Vancomycin, Teicoplanin	Reprogramming peptidoglycan biosynthesis
Tetracyclines	Minocycline, Tigecycline	Monooxygenation, efflux, altered target
Macrolides	Erythromycin azithromycin	Hydrolysis, glycosylation, phosphorylation, efflux, altered target
Lincosamides	Clindamycin	Nucleotidylation, efflux, altered target
Streptogramins	Synercid	Carbon-Oxygen lyase, acetylation, efflux, altered target
Oxazolidinones	Linezolid Efflux,	altered target
Phenicols	Chloramphenicol	Acetylation, efflux, altered target
Quinolones	Ciprofloxacin	Acetylation, efflux, altered target
Pyrimidines	Trimethoprim	Efflux, altered target
Sulfonamides	Sulfamethoxazole	Efflux, altered target
Rifamycins	Rifampin	ADP-ribosylation, efflux, altered target

Antibiotics	Examples	Mode(s) of resistance
Lipopeptides	Daptomycin	Altered target
Cationic	Colistin	peptides Altered target, efflux

CONCLUSION:

Rapidly emerging resistant bacteria threaten the extraordinary health benefits that have been achieved with antibiotics. This crisis is global, reflecting the worldwide overuse of these drugs and the lack of development of new antibiotic agents by pharmaceutical companies to address the challenge. Antibiotic-resistant infections place a substantial health and economic burden on the health care system and population. Coordinated efforts to implement new policies, renew research efforts, and pursue steps to manage the crisis are greatly needed.

REFERENCES:

1. Golkar Z, Bagazra O, Pace DG. Bacteriophage therapy: a potential solution for the antibiotic resistance crisis. J Infect Dev Ctries 2014; 13;8(2):129–136.
2. Gould IM, Bal AM. New antibiotic agents in the pipeline and how they can overcome microbial resistance. Virulence 2013; 4(2):185–191. The Antibiotic Resistance Crisis, Part 1: Causes and Threats
3. Wright GD. Something new: revisiting natural products in antibiotic drug discovery. Can J Microbial 2014; 60(3):147–154.
4. Sengupta S, Chattopadhyay MK, Grossart HP. The multifaceted roles of antibiotics and antibiotic resistance in nature. Front Microbiol 2013; 4:47.
5. Centers for Disease Control and Prevention, Office of Infectious Disease. Antibiotic resistance threats in the United States, 2013. April 2013. Available at: http://www.cdc.gov/drugresistance/ threat-report-2013. Accessed January 28, 2015.
6. Congressional Research Service Report. Life expectancy in the United States. March 2005. Available at: http://www.cnie.org/ nle/crsreports/05mar/RL32792.pdf. Accessed January 5, 2015.
7. Spell berg B, Gilbert DN. The future of antibiotics and resistance: a tribute to a career of leadership by John Bartlett. Clin Infect Dis 2014; 59 suppl 2:S71–S75.
8. Viswanathan VK. Off-label abuse of antibiotics by bacteria. Gut Microbes 2014; 5(1):3–4.
9. Read AF, Woods RJ. Antibiotic resistance management. Evol Med Public Health 2014; 2014(1):147.
10. The antibiotic alarm. Nature 2013; 495(7440):141
11. Lushniak BD. Antibiotic resistance: a public health crisis. Public Health Rep 2014; 129(4):314–316.
12. Gross M. Antibiotics in crisis. Curr Biol 2013; 23(24):R1063–R1065.
13. Piddock LJ. The crisis of no new antibiotics—what is the way forward? Lancet Infect Dis 2012; 12(3):249–253.
14. Bartlett JG, Gilbert DN, Spell berg B. Seven ways to preserve the miracle of antibiotics. Clin Infect Dis 2013; 56(10):1445–1450.
15. Michael CA, Dominey-Howes D, Labbate M. The antibiotic resistance crisis: causes, consequences, and management. Front Public Health 2014; 2:145.
16. Rossolini GM, Arena F, Pecile P, Pollini S. Update on the antibiotic resistance crisis. Clin Opin Pharmacol 2014; 18:56-60.
17. Van Boeckel TP, Gandra S, Ashok A. Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data. Lancet Infect Dis 2014; 14(8):742–750.
18. Luyt CE, Brechot N, Trouillet JL, Chastre J. Antibiotic stewardship in the intensive care unit. Crit Care 2014; 18(5):480.
19. Gelles D. Merck in $8.4 billion deal for Cubist, big maker of antibiotics. New York Times. December 8, 2014. Available at: http:// dealbook.nytimes.com/2014/12/08/merck-agrees-to-acquiredrug-maker-cubist-for-9-5-billion. Accessed January 5, 2015.
20. Itani KM, Shorr AF. FDA guidance for ABSSSI trials: implications for conducting and interpreting clinical trials. Clin Infect Dis 2014; 58 suppl 1:S4–S9.